FORM PTO-1390 (REV. 1-98) — U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
933-154PCT	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	09/486971

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FI98/00735	18 September 1998	19 September 1997

TITLE OF INVENTION

PHARMACEUTICAL PREPARTION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AS SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

APPLICANT(S) FOR DO/EO/US

LEHTOLA, Veli-Matti; RANTALA, Eeva-Maria Susanne; RANTALA, Pertti

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)) (appln. encl. W099/15155)
   - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☒ has been transmitted by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(3)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
   - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98./International Search Report with cited references
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

    1.) Zero (0) Sheets of Formal Drawing

514 Rec'd PCT/PTO 06 MAR 2000

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
NEW 09/486971	PCT/FI98/00735	933-154PCT

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):

		CALCULATIONS	PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$970.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$840.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$690.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$670.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 970.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	10 - 20 =	------	X $18.00	$	--------
Independent Claims	2 - 3 =	-------	X $78.00	$	-------
MULTIPLE DEPENDENT CLAIM(S) (if applicable)	None		+ $260.00	$	-------
TOTAL OF ABOVE CALCULATIONS =				$	1100.00
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	--------
SUBTOTAL =				$	1100.00
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	--------
TOTAL NATIONAL FEE =				$	1100.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	--------
TOTAL FEES ENCLOSED =				$	1100.00
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ **1100.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
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SIGNATURE

MURPHY, GERALD M., JR.
NAME

#28,977 (GMM)
REGISTRATION NUMBER

/GMM/sas March 6, 2000

PATENT
933-154PCT

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: LEHTOLA, Veli-Matti et al

Int'l. Appl. No.: PCT/FI98/00735

Appl. No.: New Group: Unknown

Filed: March 6, 2000 Examiner: Unknown

For: PHARMACEUTICAL PREPARTION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

March 6, 2000

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/FI98/00735 which has an International filing date of September 18, 1998, which designated the United States of America.--

IN THE CLAIMS:

CLAIM 4: Line 1, change "any one of the preceding claims" to --claim 1--

CLAIM 5: Line 1, change "any one of the preceding claims" to --claim 1--

CLAIM 6: Line 1, change "any one of the preceding claims" to --claim 1--

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

The amendment to the claims is merely to delete the improper multiple dependencies and place the application into better form prior to examination.

Docket No. 933-154PCT

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By ______________________________
Gerald M. Murphy, Jr., #28,977

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GMM/sas
933-154PCT

(Rev. 01/08/2000)

PHARMACEUTICAL PREPARATION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

The object of the present invention is a pharmaceutical preparation for oral use, especially a tablet, which as its active ingredient contains a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, i.e. a clodronate, especially disodium clodronate, and which as an excipient contains silicified microcrystalline cellulose. Further objects of the invention are a process for the manufacture of said pharmaceutical preparation, and the use of silicified microcrystalline cellulose for the manufacture of said pharmaceutical preparation.

Clodronate or the disodium salt of dichloromethylene bisphosphonic acid, tetrahydrate, is useful for instance in the treatment and prophylaxis of disorders of the calcium metabolism, such as bone resorption, hypercalcaemia and osteoporosis. Based on its ability to form a strong complex with a Ca^{2+}-ion, clodronate removes excessive calcium from the circulation, prevents calcium phosphate from dissolving from the bone and/or acts via cell-mediated mechanisms.

Clodronate has previously been administered orally in the form of conventional compressed tablets or capsules. Such a tablet or capsule disintegrates in the stomach of the patient and releases the active agent, which in the acidic environment of the stomach is converted to the free acid form. As clodronic acid is relatively poorly absorbed, the bioavailability of the active agent will be low and consequently clodronate has to be administered in relatively large doses for a prolonged time. A problem with clodronate preparations has therefore been how to achieve a sufficiently high amount and concentration of the active agent in a capsule or tablet, without having to use capsule or tablet sizes which are unpleasantly large for the patient.

Another problem with clodronate preparations has been that it is very difficult to mix untreated clodronate raw material to a homogenous mixture with other excipients and active agents present in the preparation. For example EP 275 468 discloses a process wherein clodronate raw material and excipients are mixed dry, a

granulating liquid is added, the mixture is wet granulated and the granulate is dried. Due to the properties of clodronate, the clodronate powder thus obtained is, however, inaccurate as regards its composition and obviously difficult to handle (sticky, very poor flow properties). It is thus very difficult in practice to mix it with other substances used in the preparation, as well as to further process it, wherefore, for instance, a relatively large amount of gliding agents is needed. From the homogenous raw powder an unhomogenous and poorly flowing product mass is then obtained, which affects also the accuracy of dosing of the final medicament.

The above mentioned problem relating to clodronate raw material has partly been solved by the process described in WO 95/13054, wherein clodronate is crystallized specifically as the disodium clodronate tetrahydrate which is subsequently dry granulated by compressing in such a way that the crystal structure of the disodium clodronate tetrahydrate is preserved. The process is said to lead to ready-to-use granules of uniform quality and good handling characteristics wherefore excipients are needed in considerably smaller amounts than in the previous methods. However, it does not solve the problems relating to the preparation of clodronate dosage forms by wet granulation.

Wet granulation is widely used in the pharmaceutical industry in the preparation of solid dosage forms due to the advantages it offers compared to dry granulation and direct compression. Usually the amount of excipients needed in wet granulation is less than that required for direct compression, and thus an acceptably sized tablet may be obtained. Wet granulation also provides the material to be compressed with better wetting properties and the particles comprising the resulting granulate with optimized particle size and shape. Also the amount of drug in the granules is approximately the same, and thus the content uniformity of the final preparation is generally improved.

Microcrystalline cellulose is a common excipient used in formulations which are wet granulated prior to tabletting. It is suitable not only for adding bulk to the

finished product but also has additional features that facilitate pellet formation. Unfortunately the exposure of microcrystalline cellulose to moisture in the wet granulation process severely reduces the compressibility of this excipient. This is particularly problematic in cases where a pharmaceutical preparation with a high dose of the active agent, such as in the case of clodronate, is desired as the loss of compressibility of the microcrystalline cellulose means that a larger amount of this excipient is needed to obtain an acceptably compressed final product. This in turn adds bulk, making the final product more difficult to swallow and thus reducing patient compliance.

According to the invention it has now been discovered that it is possible to achieve oral dosage forms of clodronate with acceptable size and uniform quality, however, with sufficiently high amount and concentration of the active agent in the preparation. In the preparation process of the novel oral dosage form of clodronate it is possible to use not only dry granulation but also wet granulation and direct compression techniques. This is achieved if the pharmaceutical preparation is an oral dosage form comprising easily compactible silicified microcrystalline cellulose as an excipient.

Silicified microcrystalline cellulose used in the preparation according to the invention is microcrystalline cellulose which has been coprocessed with from about 0.1 to about 20 % silicon dioxide, SiO_2, based on the amount of microcrystalline cellulose. It is an agglomerate of microcrystalline cellulose and silicon dioxide in which the microcrystalline cellulose and silicon dioxide are in intimate association with each other. This means that the silicon dioxide has been integrated with the microcrystalline cellulose particles but there is no chemical interaction between the two materials. In practice this is achieved e.g. by spray-drying a suspension of microcrystalline cellulose and silicon dioxide.

The advantage of the use of silicified microcrystalline cellulose in clodronate preparations is overall improved functionality in terms of e.g. powder flow, compactibility, tablet strength and especially reduced friability. Solid dosage forms

containing high load of clodronate are now obtainable by direct compression, dry granulation or wet granulation technique. The amount of the silicified microcrystalline cellulose which must be used in the preparation process to obtain an acceptable solid dosage form is substantially reduced, compared to the amount of usual microcrystalline cellulose which must be used for the same purpose. This naturally results in substantial reduction in tablet size. The solid clodronate preparations according to the invention are also of uniform quality and possess excellent disintegration and dissolution properties.

Extensive friability has been a problem especially with tablets containing clodronate. Extensive friability means that tablets are easily crumbled or split into pieces. Surprisingly, this problem can also be overcome by the use of silicified microcrystalline cellulose. A person skilled in the art would expect that the silicon dioxide in the silicified microcrystalline cellulose functions the opposite way when used in clodronate preparations, i.e. that it would decrease crushing strength and increase friability as gliding agents usually do.

However, one of the advantages of the use of silicified microcrystalline cellulose for the manufacture of clodronate preparations is that the silicon dioxide of the silicified microcrystalline cellulose may also function as a gliding agent while it also improves the properties of the microcrystalline cellulose.

In the process of preparing clodronate tablets containing silicified microcrystalline cellulose, it is also possible to first granulate clodronate (either by wet granulation or dry granulation technique) and then to mix the dry granules with silicified microcrystalline cellulose and, if desired, with other excipients before direct compression of the mixture into tablets. This process is technically very feasible and provides clodronate tablets with all the advantages mentioned above.

Further advantages of the use of silicified microcrystalline cellulose for the manufacture of clodronate preparations, especially clodronate tablets, are an increase in the production rate and, consequently, a technically and economically feasible

production process. Tablets containing clodronate and usual microcrystalline cellulose can be formed into tablets only at very low rates compared to tablets containing clodronate and silicified microcrystalline cellulose. The use of silicified microcrystalline cellulose enables the production rates to be increased considerably without adversely affecting the quality of tablets, as is shown in Example 8.

If desired, also other excipients in addition to silicified microcrystalline cellulose may be used in the solid dosage forms according to the invention. These excipients are known to a person skilled in the art, and their use in the manufacture of clodronate preparations has been disclosed e.g. in EP 336 851, US 3,683,080 and US 4,234,645.

Consequently, the preparation according to the invention may further comprise conventional gliding agents and lubricants, such as stearic acid or its salts (Mg-, Ca-), talc, starch, or a mixture of two or more gliding agents. If desired, also additional colloidal silica may be added in addition to what is included in the silicified microcrystalline cellulose.

Filling agents (weight balancing agents) which may be used are for example lactose, starch or its derivatives, mannitol, glucose, saccharose, microcrystalline cellulose, or a mixture of two or more filling agents. Also natural or artificial flavouring and sweetening agents may be used.

If desired, also disintegrants can be added to the preparation. These are disintegrants generally known in the art, such as for example cross-linked sodium carboxymethylcellulose, starch or its derivatives, croscarmellose, crospovidone, or mixtures of two or more disintegrants.

By using certain excipients one can also regulate, if desired, whether a preparation is to decompose in the stomach or only later in the gastrointestinal tract, and also the dissolving rate. Thus the preparation can be coated with as such known film forming agents, which dissolve at the desired pH, such as for example with

shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate or various acryl and methacryl acid derivatives. Film forming agents are known to a person skilled in the art and are commercially available.

The composition comprising clodronate and silicified microcrystalline cellulose is suitable for administration not only as a tablet but also as a number of different formulations. Thus it can for example be filled in capsules, or used as granules or a powder according to the methods generally known in the art, and further coated, if desired. Especially preferred are tablets and capsules.

The amount of clodronate in the drug delivery form according to the invention can vary within wide limits, e.g. from 10 to 95 % by weight, being typically 50 to 90 % by weight. The amount of silicified microcrystalline cellulose can vary e.g. from about 1 to about 50 % by weight, being typically from about 5 to about 25 % by weight. Preferably the preparation according to the invention comprises 60 to 80 % by weight of anhydrous disodium clodronate, about 8-20 % by weight of silicified microcrystalline cellulose, and 0.5-10 % other excipients such as lubricants and disintegrants.

The following examples illustrate the invention without limiting the same.

Example 1

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	205 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

The silicified microcrystalline cellulose used (Prosolv 90, Mendell, USA) had a 2 % w/w silicon dioxide concentration.

In the first stage of the tablet preparation, the dry granulated clodronate was moistened with stearic acid in ethanol and then dried at about 30 °C to a moisture content of appr. 18.5 - 20 %. The dried granules were then sieved through a 1.5 mm sieve. Thereafter the clodronate-stearic acid granules were mixed with carmellose sodium, silicified microcrystalline cellulose and magnesium stearate. The mixture was formed into tablets in a tabletting apparatus, using 9 x 20 mm punches to form tablets of a mean weight of 1177 mg (± 2.5 %) and of a suitable strength, for example 4 - 10 kg.

If desired, the prepared tablets may be coated with a coating solution, the composition of which per tablet may be for example the following:

Methyl hydroxypropylcellulose phthalate	42.8 mg
Diethyl phthalate	6.4 mg
Ethanol	q.s.
Purified water	q.s.

Example 2

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	155 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

The tablets were prepared essentially as described in Example 1, using the same kind of silicified microcrystalline cellulose as in Example 1.

Example 3

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	155 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

The silicified microcrystalline cellulose used (Prosolv 50, Mendell, USA) had a 2 % w/w silicon dioxide concentration. The tablets were prepared essentially as described in Example 1.

Example 4

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	140 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	8 mg

The silicified microcrystalline cellulose used (Prosolv 90, Mendell, USA) had a 2 % w/w silicon dioxide concentration. The tablets were prepared essentially as

described in Example 1, with the exception that stearic acid was dissolved in polyvinylpyrrolidone instead of ethanol.

Example 5

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	125 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

The tablets were prepared essentially as described in Example 1, using the same kind of silicified microcrystalline cellulose as in Example 1.

Example 6

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	132 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

The tablets were prepared essentially as described in Example 1, using the same kind of silicified microcrystalline cellulose as in Example 1.

Example 7

Tablets were prepared with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding anhydrous disodium clodronate	800 mg
Silicified microcrystalline cellulose	165 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

The silicified microcrystalline cellulose used (Prosolv 50, Mendell, USA) had a 2 % w/w silicon dioxide concentration. The tablets were prepared essentially as described in Example 1, using tabletting speeds as indicated in Table 1. The results from the measurements of crushing strength and friability are also shown in Table 1.

Table 1. Crushing strength and friability of tablets according to Example 7, prepared at different tabletting speeds

Tabletting speed	Crushing strength	Friability
30 000 tablets/h	16 kp	0.11 %
40 000 tablets/h	18 kp	0.20 %

Example 8

Tablets having the same composition as the tablets prepared in Example 6 were prepared at different tabletting speeds. For comparison, tablets were also prepared at different tabletting speeds with the following composition per tablet:

Disodium clodronate tetrahydrate 1000 mg responding	
anhydrous disodium clodronate	800 mg
Microcrystalline cellulose (Emcocel 50 M)	132 mg
Carmellose sodium	22 mg
Stearic acid	15 mg
Magnesium stearate	8 mg

Crushing strength and friability of the obtained tablets were measured. The results are shown in Table 2.

Table 2. Crushing strength and friability of tablets containing silicified microcrystalline cellulose (A) and of tablets containing usual microcrystalline cellulose (B). Tablets were prepared at different tabletting speeds as indicated in Table 2.

Tabletting speed	Strength of tablets A	Strength of tablets B	Friability of tablets A	Friability of tablets B
15 000 tabl/h	np	13 kp	np	3.0 %
30 000 tabl/h	18 kp	11 kp	0.39 %	38.0 %
50 000 tabl/h	18 kp	*	2.50 %	*

np not performed * could not be tabletted

Tablets containing usual microcrystalline cellulose could not be tabletted using a higher tabletting speed than 30 000 tablets/h, because tablets would have broken up.

Claims

1. Pharmaceutical preparation containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, **characterized** in that it is an oral solid dosage form comprising silicified microcrystalline cellulose.

2. Preparation according to claim 1, **characterized** in that it comprises 5-25 % by weight of silicified microcrystalline cellulose.

3. Preparation according to claim 1, **characterized** in that it comprises
a) from about 60 to 80 % by weight of anhydrous disodium clodronate;
b) from about 8 to 20 % by weight of silicified microcrystalline cellulose; and
c) from about 0.5 to 10 % by weight of lubricants and/or disintegrants.

4. Preparation according to any one of the preceding claims wherein silicon dioxide is present in the silicified microcrystalline cellulose in an amount of from about 0.1 to 20 % by weight, based on the weight of the microcrystalline cellulose.

5. Preparation according to any one of the preceding claims, **characterized** in that it is a tablet or capsule.

6. Preparation according to any one of the preceding claims, **characterized** in that the salt of dichloromethylene bisphosphonic acid is the disodium salt.

7. Process for the manufacture of a pharmaceutical preparation according to claim 1 **characterized** in that a wet granulation technique is used.

8. Process for the manufacture of a pharmaceutical preparation according to claim 1, **characterized** in that a dry granulation technique is used.

9. Process for the manufacture of a pharmaceutical preparation according to claim 1, **characterized** in that a direct compression technique is used.

10. Use of silicified microcrystalline cellulose for the manufacture of a pharmaceutical preparation containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid.

Attorney Docket No.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

933-154P

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PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: Pharmaceutical preparation comprising clodronate as active ingredient and silicified microcrystalline cellulose as excipient

Insert Title:

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,
the specification was filed on _____ as
United States Application Number _____;
and amended on _____ (if applicable)I and/or
the specification was filed on September 18, 1998 as PCT
International Application Number PCT/FI98/00735; and was
amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
973733 (Number)	Finland (Country)	9/19/1997 (Month/Day/Year Filed)	☒ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

Insert Provisional Application(s): (if any)

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application Number	Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Insert Prior U.S. Application(s): (if any)

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)

COPY

933-154P
Attorney Docket No.

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

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PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING: ↓

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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